

Survival Benefit of Extended D2 Resection for Proximal Gastric Cancer

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Background: The long-term survival of patients with adenocarcinoma of the proximal stomach remains dismal. Despite its increasing frequency and poor prognosis, a general consensus has not been reached on the extent of surgical resection. The significance of extended lymph node dissection (D2 gastrectomy) for the surgical treatment of patients with proximal gastric cancer was evaluated.

Methods: Sixty-two patients who underwent a potentially curative total or proximal gastric resection were retrospectively divided by extent of lymphadenectomy into two groups: the extended resection group (D2,D2.5) and limited resection group (D1,D1.5). Survival rates were estimated by the method of Kaplan and Meier [J Am Stat Assoc 53:457–486, 1958] and the differences compared by the log rank test. Multivariate analysis of prognostic parameters was performed using the Cox proportional hazard model.

Results: The median overall survival time for the extended resection group (D2,D2.5) was 34 months compared to 18 months for patients treated by a more limited resection (D1,D1.5). Patients treated with extended resection had an estimated 5-year overall survival rate of 37% compared to 21% for patients treated with limited resection. This difference was statistically significant with a *P* value of 0.04. The median disease-free interval for the extended resection group was 31 months compared to 17.6 months for patients in the limited resection group. The 5 year disease-free survival rate for both groups was 37% and 17%, respectively (*P* = 0.09). Extent of lymphadenectomy and stage of disease were found to be independent predictors of overall and cancer-free survival.

Conclusions: Patients treated with an extended lymph node dissection (D2 gastrectomy) were more likely to survive 5 years, had longer disease-free intervals, and prolonged median survival times (particularly patients with T1-3,N0-1,M0 cancers) as compared to those patients treated with a more limited lymph node dissection (D1,D1.5). These differences reached or approached statistical significance.

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INTRODUCTION

The frequency of proximal gastric cancer specifically of the esophago-gastric junction and cardia has significantly increased compared with cancers in other regions of the stomach. Hansson and others [1,2] have shown that the incidence of adenocarcinoma of the cardia is rising both relative to the incidence of distal gastric cancers and in absolute numbers. Although this increase has been taking place over the last three decades, the number of distal gastric cancers has markedly decreased. Cancers in the proximal location show a marked male predominance, (particularly for white men) with a male:female ratio of 4:1 [1]. For all other gastric cancers, the male:female ratio is on the order of 1.9:1. Adenocarcinoma of the proximal stomach is now among the 15 most common cancers in white men with an annual incidence of 5.8/100,000 [2]. Kalish and associates [3] suggest that there is a connection between cancer of the cardia, cigarette smoking, and alcohol consumption. This etiologic association, well recognized for other tumors of the upper aero-digestive tract, distinguishes proximal gastric cancers as an entity separate from the more distal gastric cancers, where this association is not well established. Likewise, atrophic gastritis often seen in conjunction with distal gastric cancers, is a much less frequent occurrence associated with cancers of the proximal stomach [4,5].

The long-term survival of patients with adenocarcinoma of the proximal stomach is poor [6–8]. The presence of a complex lymphatic drainage system in close proximity to the diaphragm along with the high propensity to the development of lymph node metastases renders curative surgical resection a difficult task. Although a variety of surgical approaches have been advocated, there is no general agreement on the optimum surgical strategy for treating adenocarcinoma of the proximal stomach [9–11]. The treatment currently accepted in the United States limits surgery to removal of the primary tumor along with its immediately adjacent lymph nodes (D1 gastrectomy), hoping that adjuvant therapy might destroy residual disease [12]. Reports of the application of systematic extended lymph node dissection (D2 gastrectomy) for the surgical treatment of proximal gastric cancer are rare in the West and primarily limited to the Japanese literature [13]. The purpose of this retrospective study was to analyze and compare the outcome of patients treated with a standard D1 gastrectomy to those treated with en bloc removal of the primary tumor and extended lymph node dissection (D2 gastrectomy).

MATERIALS AND METHODS

The medical records of 62 patients with a histologic diagnosis of adenocarcinoma of the proximal stomach

TABLE I. Lymphadenectomy for Proximal Gastric Cancer

Gastric resection	Lymph node groups to be removed		
	D1	D2	D3
Total gastrectomy	1–6	1–11	1–16
Proximal gastrectomy	1–4	1–11	1–16 ^a

^aIncluding lower mediastinal lymph nodes.

registered at Roswell Park Cancer Institute (RPCI) between 1975 and 1992, who underwent a potentially curative gastric resection, were reviewed. Gastric resections were defined by the extent of lymph node dissection according to the General Rules for the Gastric Cancer Study in Surgery and Pathology of the Japanese Research Society for Gastric Cancer [14]. Gastric resections in this study were classified as D1, D1.5, D2, and D2.5. For purposes of comparison, resections were retrospectively divided into two groups, the limited resection group (D1,D1.5) and extended resection group (D2,D2.5). All patients were treated with either a proximal gastrectomy, usually an Ivor-Lewis esophagogastric resection, or a total gastrectomy. The locations of the proximal gastric carcinomas were identified by esophagogastroduodenoscopy and classified as esophagogastric (EG) junction, cardia, or fundus. The cardia was defined as that portion of the stomach within 3 cm of the esophagogastric junction. Gastric carcinomas were staged according to the revised 1987 TNM classification [15]. Table I indicates the lymph node groups that were removed with each type and extent of gastric resection. These lymph node groups correspond to the regional lymph nodes of the stomach as outlined in the general rules (Table II).

Survival curves were generated for both groups by the method of Kaplan and Meier [16,17] and compared by the log rank test. Prognostic factors, including age, gender, stage of disease, histologic type, grade, type of resection, extent of lymphadenectomy, tumor location, and lymph node status, were entered into the Cox proportional hazards model for multivariate analysis [17]. A *P* value of less than or equal to 0.05 was considered to be statistically significant.

RESULTS

The study included 57 males and 5 females. The median age was 60 years (range, 33–85 years). The median follow-up period was 26 months. Thirty-nine of the 62 gastric cancers were located at the EG junction, 20 in the gastric cardia, and 3 were in the fundus. The majority of gastric cancers were adenocarcinomas (54 patients), whereas seven were signet ring carcinomas, and one an

TABLE II. Regional Gastric Lymph Node Grouping*

Group	Location
1	Right cardiac
2	Left cardiac
3	Lesser curvature
4	Greater curvature
5	Suprapyloric
6	Infrapyloric
7	Left gastric artery
8	Common hepatic artery
9	Celiac axis
10	Splenic hilum
11	Splenic artery
12	Hepatic pedicle, HDL ^a
13	Retropancreatic
14	Mesenteric root
15	Middle colic artery
16	Para-aortic

*From the Japanese Research Society for Gastric Cancer. The General Rules for Gastric Cancer Study in Surgery and Pathology [14].

^aHepatoduodenal ligament.

undifferentiated carcinoma. There were 53 esophagogastrectomies (including one transhiatal resection), and nine total gastrectomies. Of these, 18 resections were considered D1, 23 were considered D1.5, 20 were considered D2, and one was considered a D2.5 resection. Forty-five patients (73%) were found to have lymph node metastases in their operative specimen. The remaining 17 patients had node negative (N0) proximal gastric adenocarcinoma. Of the 45 patients with lymph node metastases, 27 were found to have N1 lymph node metastases [metastases confined to perigastric lymph nodes within 3 cm of the primary cancer], whereas 18 patients had N2 lymph node involvement (metastases in regional lymph nodes >3 cm from the primary cancer, or along left gastric, common hepatic, splenic or celiac arteries). Half the patients were classified as Stage III, 17 (27%) were stage IIIA [T2-4 N0-2 M0], 14(23%) were stage IIIB [T3-4 N1-2 M0], 18 (29%) were stage II [T1-3 N0-2 M0], and 13 (21%) were stage I [T1-2 N0-1 M0].

The estimated 5-year overall survival rate for the entire group was 27% with a median survival of 25 months. The median overall survival of the extended resection group (D2,D2.5) was 34 months as compared to only 18 months for the limited resection group (D1,D1.5). The estimated overall 5-year survival rate for both groups was 37% and 21%, respectively. This difference was statistically significant with a *P*-value of 0.04 and is illustrated in Figure 1. Figure 2 demonstrates the difference in disease-free survival between the two groups. Patients treated by extended resection had an estimated 5-year disease-free survival rate of 37% and a median survival of 31 months, as compared to 17% and 17.6 months respectively, for those treated by limited resec-

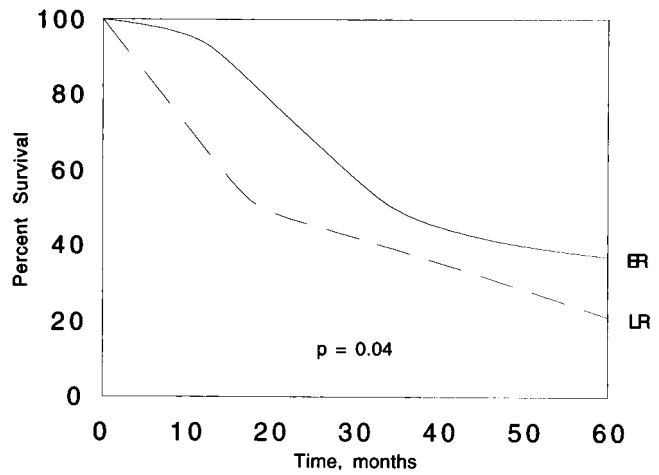


Fig. 1. Overall survival rates for the two resection groups. The difference in survival between the two curves is statistically significant. ER, extended resection; and LR, limited resection.

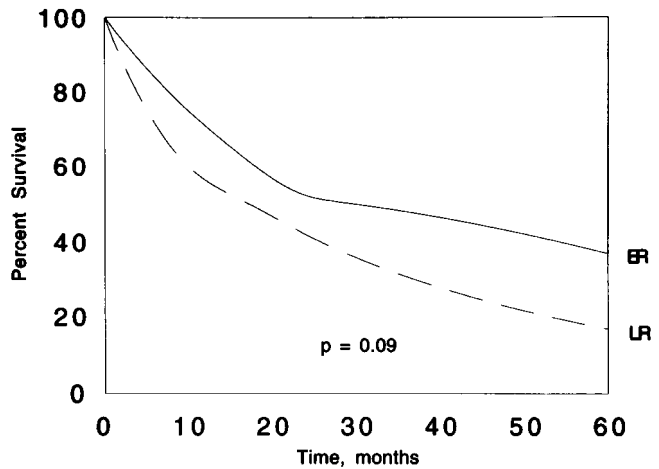


Fig. 2. Comparison of disease-free survival between the extended resection group, ER and limited resection group, LR.

tion (*P* = 0.09). For patients with T1-3,N0-1,M0 proximal gastric adenocarcinoma (cancer invades lamina propria, submucosa [T1], cancer invades muscularis propria or subserosa, but does not penetrate the serosa [T2], cancer penetrates the serosa, but does not invade adjacent organs [T3]), Figure 3 illustrates the survival curves achieved by both groups. The median survival time of the extended resection group was 52 months vs. 21 months for the limited resection group. No deaths occurred in the extended resection group during the time between that group's median survival of 52 months and 60 months resulting in a 5-year overall survival rate of 50%. This compares favorably to the 23% 5-year overall survival rate for patients treated with limited resection (*P* = 0.02).

Table III provides the median survival times, as well

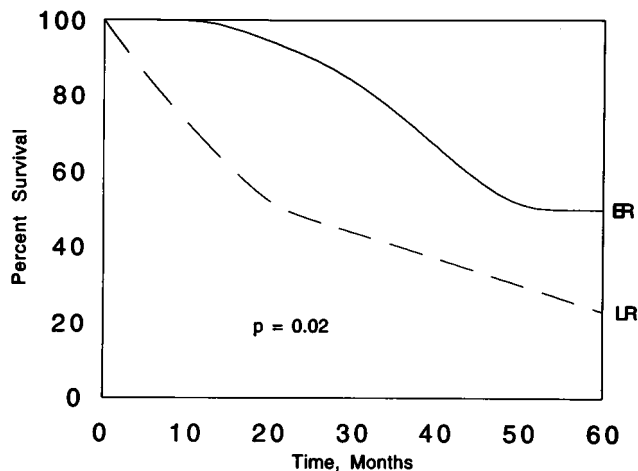


Fig. 3. Overall survival rates for patients with T1-3,N0-1,M0 proximal gastric cancers. ER, extended resection; and LR, limited resection.

as the estimated 1-year, 2-year, and 5-year overall survival rates for the four types of extent of resections performed in this study. The estimated 5-year overall survival rate of the D2 resection group was triple that of the D1 resection group (35% vs. 11%, $P = 0.03$).

Stage of disease ($P = 0.001$), lymph node status ($P = 0.02$), and extent of resection ($P = 0.04$) were found to be statistically significant predictors of overall and cancer-free survival as determined by univariate analysis. After multivariate analysis only extent of resection ($P = 0.009$) and stage of disease ($P = 0.01$) emerged as independent predictors of overall survival and freedom from cancer recurrence.

DISCUSSION

The results of surgical treatment for resectable adenocarcinoma arising from the proximal stomach suggest a bleak outlook. Cancers of the proximal stomach are more likely to have lymph node metastases, present with an advanced stage of disease, and are less amenable to curative resection compared to distal gastric cancers [18]. Despite its increasing incidence worldwide, a consensus on the standard surgical treatment of proximal gastric cancer remains elusive. Current treatment strategy adopted by many Western surgeons limits the role of surgery to resection of the primary tumor and the immediately adjacent lymph nodes. This strategy embodies the concept of biologic predeterminism, i.e., the outcome of treatment is determined by the biologic behavior of the cancer and removing more than the primary tumor is not helpful [19]. In this strategy, lymph node metastases are considered indicators of disseminated disease and dissection of more distal lymph nodes is not thought to be beneficial [20]. Proponents of this surgical strategy believe that an extended resection will result in the same survival as that obtained with a limited resection of the primary tumor.

The Upper Gastrointestinal Service at RPCI has believed for many years that en bloc D2 resections for gastric carcinoma could be beneficial. In the early 1970s, a group of visiting Japanese surgeons brought us a copy of the general rules. Shortly thereafter, gastric resections at RPCI were organized according to the planned systematic extended lymph node dissections as outlined in the general rules and popularized by Japanese surgeons. Although we were not always rigorous in following these rules, patients with extensive disease were more likely to receive an extended operation. A recent retrospective review of our own data suggested that patients treated with an extended D2 resection received a significant survival advantage over those treated with less than a D2 resection [21]. As the proportion of our patients with proximal gastric cancer rapidly increased while their prognosis, as traditionally managed was poor, we felt it was critically important to assess the benefit of extended lymph node dissection in this group of high risk patients referred to our service. Patients with adenocarcinoma of the proximal stomach were retrospectively divided into two groups, according to extent of operation (D2 or greater compared to less than a D2 resection). Their survival data were analyzed and compared. Only procedures with curative intent were included in this study.

Our results demonstrated a marked improvement in the overall and disease-free 5-year survival rates for patients treated with a D2 or greater resection compared to those treated with a lesser resection (D1,D1.5). Patients with T1-3,N0-1,M0 gastric cancers had a median survival time of >4 years compared to <2 years for those treated with a limited resection (Fig. 3). The fact that patients treated with a D2 resection had a 5-year survival rate three times that of the group treated with a D1 resection strongly supports the efficacy of extended lymph node dissection in the treatment of adenocarcinoma of the proximal stomach (Table III). Extent of resection proved to be the most important independent prognosticator of overall and disease-free survival.

Critics of the D2 resection claim that the supposedly superior survival rates of patients treated with an extended resection is merely due to stage migration or the "Will Rogers" phenomenon [22]. Resection of lymph nodes that contain metastatic carcinoma are upstaged (e.g., stage I to stage II and stage II to stage IIIA or IIIB) leaving a better population of patients in the lower stages, according to this philosophy. Removing more lymph nodes only improves staging accuracy, but not patient survival. Bad prognosis stage I patients become good prognosis stage II patients, bad prognosis stage II patients become good prognosis stage III patients. The overall effect of stage migration is that survival in both lower and upper stages is improved simply by shuffling the patients from one stage to another. Advocates of stage migration argue that this occurs without actually

TABLE III. Estimated Survival Rates According to Extent of Resection for Gastric Cancer*

Extent of resection	N	Med survival (mos)	Estimated survival rates (%)		
			1 yr	2 yr	5 yr
D1 ^a	18	12	61	39	11
D1.5 ^a	23	25	70	52	29
D2 ^b	20	34	95	69	35
D2.5 ^b	1	Alive	disease-free at 34 months		

*P-value = 0.03, comparing D2 vs. D1 for estimated 5-year survival rate.

^aLimited resection.

^bExtended resection.

improving the survival otherwise obtained with a D1 resection. If this is true, then D1 resected stage I patients and D2 resected stage I patients should have similar survival rates. Conversely, if stage migration is not the source of improved survival, then the survival of D2 resected stage I patients might differ from that of D1 resected stage I patients, and it does. In our study, D1 resected stage I patients had an estimated 5-year survival rate of 40%, whereas the D2 resected stage I patients had a 5-year survival rate of 83% and their median survival has not yet been reached.

Currently there are three prospective randomized trials of R1 vs. R2 gastrectomy for gastric carcinoma in progress to evaluate the wider application of this procedure: the British Medical Research Council Cooperative Surgical Trial for Gastric Cancer, the Netherlands D1/D2 Gastric Carcinoma Study, and the Capetown Trial in South Africa [23]. The first two trials are multicenter studies and the survival results of both studies are not yet available. In a preliminary report from the Dutch study, Bonenkamp [24] reported that the operative mortality rate of the D2 resection was twice that of the D1 resection. In the Capetown trial, Dent and associates [23] found no survival advantage for the D2 gastrectomy compared to the D1 procedure. However, they confined their study to T1-3, N0-1, M0 gastric cancers, and the trial lacks significant statistical power due to the small number of patients studied (35 patients were randomized to the D1 arm and 31 patients to the D2 arm).

CONCLUSION

Our findings appear to support the concept of extended resection (D2 or greater) as the initial surgical treatment of choice in patients with adenocarcinoma of the proximal stomach. Patients with both early and late stages of disease have accrued a survival advantage from the extended D2 gastrectomy. Until the results are available from the larger multicenter studies and confirmatory studies are undertaken, we believe that the D2 gastrectomy performed according to the General Rules for the Gastric Cancer Study in Surgery and Pathology of the Japanese Research Society for Gastric Cancer might en-

hance the cure of the patient with gastric carcinoma of the proximal stomach.

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